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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,905	10/05/2005	Oliver Schadt	MERCK-3075	6249

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EXAMINER	
JARRELL, NOBLE E	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
12/01/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,905	SCHADT ET AL.	
	Examiner	Art Unit	
	NOBLE JARRELL	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-9,11 and 13-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-9,11 and 13-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12 August 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Current Status of 10/551905

1. The rejections under 35 U.S.C. 112 2nd paragraph and 35 U.S.C. 102 have been overcome by the amendment filed 12 August 2009.

2. Claims 1, 3, 4, 6-9, 11, and 13-23 are pending in the instant application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Newly amended claims 11, 13, 16, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vitro* inhibition of 5-HT_{2A} receptors, does not reasonably provide enablement for treatment or prevention of disorders associated with 5-HT_{2A}. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention:

The claims are drawn to the treatment of disorders related to modulation of 5-HT_{2A} receptors using compounds composed of pyrazole ring bonded to a phenyl or pyridine ring through the 1-position of the pyrazole ring. In the same compound, the 5-position of pyrazole ring is modified with a $(CH_2)_{0-6}$phenyl moiety or a $(CH_2)_{0-6}$heterocycle moiety. Thus, the claims taken together with the specification imply that these compounds can treat disorders related to 5-HT_{2A} receptor modulation.

(2)The breadth of the claims:

The extremely diverse range of sleep disorders covers Dyssomnias, Parasomnias, Medical/Psychiatric Sleep Disorders and others. First there are the Intrinsic Sleep Disorders, including Psychophysiological Insomnia, Sleep State Misperception, Idiopathic Insomnia, Narcolepsy, Recurrent Hypersomnia, Idiopathic Hypersomnia, Posttraumatic Hypersomnia, Obstructive Sleep Apnea Syndrome, Central Sleep Apnea Syndrome, Central Alveolar Hypoventilation Syndrome, Periodic Limb Movement Disorder, Restless Legs Syndrome, and Intrinsic Sleep Disorder NOS. Second there are the Extrinsic Sleep Disorders, including Inadequate Sleep Hygiene, Environmental Sleep Disorder, Altitude Insomnia, Adjustment Sleep Disorder, Insufficient Sleep Syndrome, Limit-Setting Sleep Disorder, Sleep-Onset Association Disorder, Food Allergy Insomnia, Nocturnal Eating (Drinking) Syndrome, Hypnotic-Dependent Sleep Disorder, Stimulant-Dependent Sleep Disorder, Alcohol-Dependent Sleep Disorder, Toxin-Induced Sleep Disorder, and Extrinsic Sleep Disorder NOS. Third, there are Circadian Rhythm Sleep Disorders, including Time Zone Change (Jet Lag) Syndrome, Shift Work Sleep Disorder, Irregular Sleep-Wake Pattern, Delayed Sleep Phase Syndrome, Advanced Sleep Phase Syndrome, Non-24-Hour Sleep-Wake Disorder, and

Circadian Rhythm Sleep Disorder NOS. Fourth, there are Arousal Disorders, including Confusional Arousals, Sleepwalking, and Sleep Terrors. Fifth, there are Sleep-Wake Transition Disorders, including Rhythmic Movement Disorder, Sleep Starts, Sleep Talking, and Nocturnal Leg Cramps. Sixth, there are Parasomnias Usually Associated with REM Sleep, including, Nightmares, Sleep Paralysis, Impaired Sleep-Related Penile Erections, Sleep-Related Painful Erections, REM Sleep Related Sinus Arrest, and REM Sleep Behavior Disorder. Seventh, there are Other Parasomnias, including Sleep Bruxism, Sleep Enuresis, Sleep-Related Abnormal Swallowing Syndrome, Nocturnal Paroxysmal Dystonia, Sudden Unexplained Nocturnal Death Syndrome, Primary Snoring, Infant Sleep Apnea, Congenital Central Hypoventilation Syndrome, Sudden Infant Death Syndrome, Benign Neonatal Sleep Myoclonus, and Other Parasomnia NOS. Eighth, there are Sleep Disorders Associated with Mental Disorders, including Psychoses, Mood Disorders, Anxiety Disorders, Panic Disorder and Alcoholism. Ninth, there are Sleep Disorders Associated with Neurological Disorders, including, Cerebral Degenerative Disorders, Dementia, Parkinsonism, Fatal Familial Insomnia, Sleep-Related Epilepsy, Electrical Status Epilepticus of Sleep, and Sleep-Related Headaches. Tenth, there are Sleep Disorders Associated with Other Medical Disorders, including, Sleeping Sickness, Nocturnal Cardiac Ischemia, Chronic Obstructive Pulmonary Disease, Sleep-Related Asthma, Sleep-Related Gastroesophageal Reflux, Peptic Ulcer Disease and Fibrositis Syndrome. In addition, there are an assortment of poorly defined disorders and syndromes, including Short Sleeper, Long Sleeper, Subwakefulness Syndrome, Fragmentary Myoclonus, Sleep Hyperhidrosis, Menstrual-Associated Sleep Disorder, Pregnancy-Associated Sleep Disorder, Terrifying Hypnagogic Hallucinations,

Sleep-Related Neurogenic Tachypnea, Sleep-Related Laryngospasm, and Sleep Choking Syndrome.

(3) The state of the prior art, (4) the predictability or unpredictability of the art, and (5) the quantity of experimentation necessary:

"Combating" may be interpreted as prevention ("Combat", http://www.aolsvc.merriam-webster.aol.com/dictionary/combating, accessed 20 November 2009).

Premenstrual syndrome is not curable (is not responsive to prophylaxis) ("Premenstrual Syndrome", http://www.medicinenet.com/premenstrual_syndrome/page5.html, accessed 19 September 2007, cited in previous office action).

Roth et al. (*Expert Opinion in Therapeutic Targets*, **2001**, *5(6)*, 685-95, cited previously) teach that 5-$HT_{2A/2C}$ antagonism may be linked to treatment of sleeping disorders (section 3.3, paragraph 1, page 690). This teaching suggests that future research is needed to determine if 5-$HT_{2A/2C}$ antagonism is really linked to *in vivo* treatment of diseases. The conclusion states that the 5-$HT_{2A/2C}$ receptor may be a potential avenue of treatment for a large number of common diseases including depression, anxiety, schizophrenia, OCD, and obesity. This teaching suggests that future research is needed to determine if the 5-$HT_{2A/2C}$ receptor is a viable *in vivo* target. A new generation of drugs (using a structure-based approach) will likely be developed which may revolutionize treatment for a large number of common diseases. This teaching shows two concepts: future research is needed to develop new drugs (undue experimentation) and then treatment of a disease *may* happen (unpredictability) ["conclusion" (section 4, page 691)].

(6) The relative skill of those in the art:

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position (MD's, PhD's, or those with advanced degrees and the requisite experience in treatment of disorders related to 5-$HT_{2A/2C}$ receptors).

(7) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for *in vitro* inhibition of 5-HT_{2A} receptors.

However, the specification does not provide guidance for treatment or prevention of sleeping disorders and schizophrenia and the prevention of premenstrual syndrome.

Considering the state of the art as discussed by the references above, particularly with regards to claims 11, 13, 16, and 18, and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

This rejection is maintained because Roth teaches that 5-HT_{2A} antagonists *may* improve sleep patterns. Thus, there is unpredictability in the treatment of sleep disorders with 5-HT_{2A} antagonists. Several possible routes are listed (page 690, section 3.3). The possibility of at least three routes suggests that future research is needed to determine the effectiveness of a route. The conclusion teaches two concepts about 5-HT_{2A} antagonists: future research is needed to develop new drugs (undue experimentation) and then treatment of a disease *may* happen (unpredictability).

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3, 4, 6, 7, 8, 9, 11, 13-16, and 18-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Variable "het" is not clearly defined in claim 1 (which all other claims depend on). In claim 1, the last group for "het" (page 8) is 5-CH_2Het-2-furyl. This group is unclear because variable "het" consists of 85 separate chemical moieties in claim 1. In the last group of this variable, a methylene group is attached to "het" ("het" is embedded within itself). Based on this embedding of "het" within the very definition of the same variable, this last group is unclear because it unclear which specific instance of "het" it stands for.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Newly amended claims 2, 3, 4, 6, 7, 8, 14, 15, 17, 20, 21, 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiemann et al. (WO 03/031435, filed 11 September 2002, cited previously).

Determining the scope and contents of the prior art

Schiemann describes the following compounds : 266,267, 269, 271, 272, 274, 281, 282, and 284 (pages 49-50) ; 316, 317, 319, 321, 322, 324, 331, 332, and 334 (pages 52-53); 366, 367, 371, 372, 374, 381, 382, and 384 (pages 56-57); 416, 417, 419, 421, 422, 424, 431, 432, and 434 (pages 59-60); 466, 467, 469, 471, 472, 474, 481, 482, and 484 (pages 62 and 63); 566, 567, 569, 571, 572, 574, 581, 582, and 584 (pages 69 and 70); 616, 617, 619, 621, 622, 624, 631, 632, and 634 (pages 72 and 73); and 666, 667, 669, 671, 672, 674, 676, 677, 681, 682, and 684 (pages 76 and 77). In these compounds, N (as variable X of 10/551905) is two atoms away from the point of attachment to the pyrazole ring and R^2 is always H. Instant variable R^6 (R^1 of WO 03/031345) is selected from the group consisting of phenyl, *p*-F-phenyl, *p*-CN-phenyl. Instant variable R^3 (R^2 of WO 03/031345) is selected from the group consisting of phenyl, *o*-CN-phenyl, or 2-pyridyl. Instant variable R^1 is CO_2Et, CH_2OH, CHO, $(CH_2)_2OH$, CH=N-OMe, CH_2-piperazine, CH_2-4-methyl-piperazine, or CH_2NH(4-methylpiperazin-1-yl). Pharmaceutical compositions containing these compounds and methods of making the same are described (claim 13, page 88; examples A through I, pages 81 and 82). Example 5 teaches the preparation of compounds of formula IA. These compounds are being used as glycine transport inhibitors for the treatment of various diseases (see abstract).

Ascertaining the differences between the prior art and the claims at issue

In instant formula I, the pyrazole ring is connected to the *ortho* position of the pyridine ring (when X is N). Schiemann prepares compounds in which a pyrazole ring is connected to the *meta* position of the pyridine ring.

Resolving the level of ordinary skill in the pertinent art

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position (MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds of the elected group).

Considering objective evidence present in the application indicating obviousness or nonobviousness

In re Norris (84 USPQ 458) teaches "Counsel for applicant in their brief acknowledge that the record herein does not establish new and useful compound defined by the rejected claim possesses one or more specifically identified properties to be recognized as unobvius or unexpected, as measured by every conceivable standard. Since the product claimed herein admittedly possesses no unexpected characteristics or properties, in view of what has hereinbefore been said, it is not patentable."

Sterling Drug Inc. v. Watson, Comr. Pats. (108 USPQ 37) teaches that the test to be applied in matter of the patentability of a compound that is a homologue of another is whether the beneficial characteristics are both unexpected and obvious.

The major difference between compounds taught by Schiemann is the point of attachment between the pyridine ring and the pyrazole ring. In the instant application, the point of attachment is the 2-position, and in Schiemann the point of attachment is the 3-position. Although compounds of Schiemann are not being used in the same disorders or receptors as the instant application, it is obvious to try these compounds because of two reasons: one, the structural difference is the point of attachment between the pyridine ring with variable X and the pyrazole ring and two, the compounds of Schiemann have therapeutic use. Example 5 shows that a reasonable expectation of success exists when the pyrazole is connected to the *meta* position of the pyridine ring. Claim 17 is rendered obvious because the 4-ethyl-piperazine is an analogue of a 4-methyl-piperazine ring. In claim 17, an ethyl group attached to the 4-position of a piperazine ring. Because these two groups only differ by CH_2, they are considered analogous to one another. As stated previously, compounds prepared by Schiemann have therapeutic use. Thus, motivation to prepare these compounds is present.

Conclusion

10. No claims are allowable.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624